Clinical Value of Calcium Antagonists in Treatment of Cardiovascular Disorders

DENNIS M. KRIKLER, MD, FACC, EDWARD ROWLAND, MB

London, England

All calcium antagonists have the ability to decrease the symptoms and signs in some patients with ischemic heart disease and help lower the blood pressure in hypertensive persons, but in clinical doses nifedipine does not exhibit antiarrhythmic properties, although these are an important part of the action of verapamil, diltiazem and some substances with a similar chemical structure. In certain disorders beta-adrenergic blocking drugs are useful adjuncts, and under some circumstances, particularly variant angina and supraventricular arrhythmias, specific calcium antagonists are the drugs of choice. More data are needed to define the role of calcium antagonists during cardiopulmonary bypass, in the protection of the ischemic myocardium, in the management of hypertrophic cardiomyopathy and in specific cases of primary pulmonary hypertension. When used with an appropriate sense of perspective and careful observation, calcium antagonists provide useful additional means of helping selected patients suffering from particular cardiovascular diseases.

It is just a century since the London physiologist and physician, Sydney Ringer (1), showed that calcium was essential for the proper function of the myocardium, and it took nearly 90 years to translate the lessons from his studies into specific therapeutic action. From their work on a series of compounds of different chemical structures, Albrecht Fleckenstein and his co-workers in Freiburg (2,3) characterized a property they called calcium antagonism. There are four possible means by which calcium may move inward across the myocardial cell membrane (4): passive transport, calcium-sodium exchange, calcium-potassium exchange and passage through the voltage-activated slow inward channel. Only the latter mechanism is inhibited by the so-called calcium antagonists, and we follow Nayler's definition (4) of these substances as having the "ability to inhibit the inward transport of Ca^{2+} through voltage-activated slow channels, an inhibitory effect that is counteracted or overcome by raising the extracellular Ca^{2+}."

Such action has many synonyms (4,5), of which, in the United States, "calcium channel blocker" now seems most popular. Whatever the general name, there are two crucial aspects: 1) possession of action as defined (1,4), and 2) avoidance of confusion with other agents that may incidentally and in other ways affect calcium transport, for example, lidoflazine, which at the membrane level is essentially an inhibitor of the fast inward, sodium-dependent channel (6).

Mechanism of Action of Calcium Antagonists

Calcium antagonists have a variety of actions on excitation-contraction coupling, tending to produce vasodilatation, reduction of force in myocardial contraction and, in certain cases, depression of impulse formation and conduction. These are basically dependent on the fact that calcium influx leads to activation of myofibrillar adenosine triphosphatase which converts phosphate-bound energy into mechanical work, with a consequent increase in oxygen requirements. Calcium antagonists, on the other hand, limit calcium entry into cardiac and smooth muscle cells, thereby reducing the splitting of adenosine triphosphate and myocardial oxygen demand; the force of myocardial (and vascular smooth muscle) contraction is concomitantly attenuated. It must be remembered, of course, that some of these actions are compensated for in the intact human heart by such means as reflex sympathetic activity, and in practice cardiac output is not significantly changed (7,8). These mechanisms have already been extensively reviewed (4,5,9) and we will later concentrate on the clinical role of the agents.

From the Cardiovascular Division, Royal Postgraduate Medical School, Hammersmith Hospital, London, England.

Address for reprints: Dennis M. Krikler, MD, Royal Postgraduate Medical School, 150 Du Cane Road, London W12 OHS, England.

0735-1097/83/010355-10$03.00

Available Agents

At present, three calcium antagonists (nifedipine, verapamil and diltiazem) are available in the United States. These drugs and others have, however, been in use elsewhere for a long time, verapamil for more than 15 years. Since Fleckenstein's pioneering laboratory studies (10) several groups of compounds have been developed, not necessarily sharing a common molecular configuration: these include the papaverine derivatives verapamil, methoxyverapamil (D600) and tiapamil; the 1,4 dihydropyridine nifedipine and several congeners; diltiazem; the diphenylamines prenylamine and fendiline; and perhexiline (2,11–16). Fleckenstein (17) recently stressed the dominant position of the three main calcium antagonists, verapamil, nifedipine and diltiazem in contrast to the less specific weaker members such as prenylamine. Because these three "major" calcium antagonists have been evaluated extensively in clinical practice, we will review aspects of their use for several indications relevant to the cardiovascular system.

Angina Pectoris

In the vast majority of patients who suffer from angina pectoris, the underlying disease is coronary arteriosclerosis, which so obstructs the artery that myocardial blood flow cannot be increased enough to cope with increased oxygen requirements such as those that occur during exercise. The benefits of nitrates and beta-receptor blocking drugs in angina tend to be effected by reducing myocardial work. Although calcium antagonists share this property, they also may increase perfusion by producing coronary vasodilatation, as demonstrated in animal studies (18–20). When there is coronary artery disease, even though coronary arteriolar resistance may be decreased at rest, evidence for an increase in coronary blood flow does exist although the data are conflicting (21,22).

A most elegant demonstration of the difference in action between calcium antagonists, nitrates and beta-receptor blocking drugs was given by Engel and Lichtlen (23), who studied 36 patients with isolated stenosis of the anterior descending or circumflex branch of the left coronary artery. All agents were given sublingually and the patients were assessed at rest and during pacing-induced ischemia. Regional myocardial blood flow was measured using xenon-133 washout at rest and during ischemia, and atrial pacing was performed at identical heart rates before and after drug administration. Nifedipine was shown to decrease peripheral resistance and also to increase myocardial blood flow by reducing coronary resistance, while nitrates reduced preload and afterload and beta-receptor blocking drugs reduced myocardial oxygen consumption by direct cardiac action. These observations were in patients with obstructive coronary disease; in addition, calcium antagonists have been shown to reverse or prevent coronary artery spasm on the basis of direct observations using coronary arteriography or inference from hemodynamic or noninvasive monitoring of patients with variant angina (24,25).

Clinical Experience in Angina

Variant and unstable angina. Angina at rest associated with ST segment changes, more usually elevation than depression, is believed often to be caused by temporary enhancement of coronary artery tone leading to varying degrees of obstruction (26). It is likewise clear that in unstable angina this factor may be operative with or without coronary arteriosclerosis (27). Remission of ischemic events is usually complete when calcium antagonists are administered to most patients shown to have spasm (24,25,28–30) and the symptoms may recur promptly if the medication is withdrawn (24,25). Impressive responses to nifedipine (29), although demonstrated without control subjects, were seen in 8 patients with variant angina whose coronary arteries were normal or only mildly abnormal, as well as in a later study of 127 patients with coronary spasm (31), in whom nifedipine decreased the frequency of anginal episodes from an average of 16 a week to 2; control proved complete in 63% of these subjects. Substantial improvement was documented elegantly in 27 patients in whom nifedipine, diltiazem and verapamil were able to block ergonovine-induced episodes of variant angina (32), and also in 4 similar subjects in another study (33) on careful titration of different doses of ergonovine. In six patients believed to suffer from coronary artery spasm on exertion, the chest pain and ST segment elevation were prevented by oral verapamil (34).

Clinical experience with variant angina also has been favorable and two controlled studies have shown good response. In 12 patients with unstable angina and frequent episodes of ST segment displacement at rest, verapamil in a dose of 480 mg/day, given during two separate treatment periods, reduced the number of episodes from 123 and 130 during treatment with placebo to 31 and 23 during drug treatment, respectively; this was a double-blind study conducted in a coronary care unit (35). An even more convincing demonstration of the value of a calcium antagonist was seen in a prospective, double-blind, randomized placebo-controlled trial in 138 patients with unstable angina; medical treatment failed in 43 of 70 patients given placebo but in only 30 of 68 given nifedipine (36).

Thus, while early results were favorable but sometimes open to question because of study design, the beneficial effects of calcium antagonists have been effectively demonstrated in variant and unstable angina (32,33,36) and it is quite clear that they have a valuable role in the management of these disorders.

Chronic stable angina. Although variant or unstable angina provides an immediate challenge requiring treatment,

most patients suffering from angina do so on a chronic basis in association with coronary artery disease, and the possibility of treatment with calcium antagonists in addition to beta-receptor blocking drugs and other measures requires careful assessment, in some cases as a possible alternative to coronary artery bypass grafting. While a few years ago there were no properly controlled clinical trials of calcium antagonists in chronic stable angina, several have been reported in recent years, and these agents now can be seen to have an important role.

While early studies using verapamil at low doses gave equivocal results (37), during double-blind clinical trials doses of 360 mg/day reduced the frequency of anginal attacks and the consumption of nitroglycerin by approximately 50% and significantly improved exercise ability (38,39). These benefits were maintained without notable adverse effects at follow-up after 1 year of treatment (40). Other studies (41) have found similar results in comparison with placebo.

Nifedipine has also been proved effective. In a single-blind controlled trial in 10 patients with chronic stable angina (42), nifedipine in a dose of 60 mg/day reduced the average frequency of attacks from 11 to 6 episodes a patient a week, and the consumption of nitroglycerin from 9 to 4 tablets a week; there was also a moderate increase in the duration of exercise that could be undertaken. In our own double-blind studies (43) on 16 patients, nifedipine in a dose of 60 mg/day reduced the frequency of attacks of angina and the number of nitroglycerin tablets consumed, respectively, from 22 to 12 episodes and from 18 to 11 tablets a week. We also demonstrated a reduction in the area of exercise-induced myocardial ischemia by 35%, as assessed by 16-point precordial electrocardiographic mapping; the number of episodes of ST depression seen on ambulatory electrocardiographic monitoring decreased by 51%. Of the episodes of ST depression, 60% had been asymptomatic, and these responded to nifedipine in exactly the same way as did episodes associated with chest pain. Somewhat larger numbers of patients were analyzed, although in less detail, in a multicenter trial of nifedipine (44) and favorable responses were of the same order.

There is every reason to believe that diltiazem is also effective in chronic stable angina, as judged by symptoms, improvement in exercise ability and amelioration of electrocardiographic changes of ischemia, using a different form of assessment: a maximal exercise test 3 hours after a single oral dose of 120 mg of diltiazem, given in double-blind fashion and compared with placebo (45). Using a protocol very similar to ours (43), others (46) have shown comparable efficacy of verapamil, 360 mg/day, and nifedipine, 60 mg/day, as judged by similar subjective and objective indexes. This is consistent with the observation that 10 mg of nifedipine and 160 mg of verapamil given orally increase exercise duration similarly when compared with placebo (47).

Combined treatment with calcium antagonists and beta-receptor blocking agents. The possibility of combining calcium antagonists and beta-adrenergic blocking drugs raises interesting implications regarding both potential benefits and risks. Our own previous adverse experience with intravenous verapamil and beta-adrenergic blocking drugs (48) and our demonstration that at clinical doses nifedipine lacks the potent electrophysiologic effects seen with varapamil (49) made us reluctant to combine verapamil with beta-receptor blocking drugs. We therefore compared the effects of nifedipine with those of propranolol, as well as the combination of both. In our study (43), we used nifedipine and propranolol at two dose levels, respectively 30 and 60 mg/day, and propranolol at levels of 240 and 480 mg/day; the smaller and larger doses of each were combined with the corresponding amounts of the other substance in crossover studies. At each dose level propranolol proved slightly more effective than nifedipine as judged from the incidence of anginal attacks, the number of tablets of nitroglycerin consumed and objective measurements of exercise-induced ST segment depression and episodes of ST segment depression during 48-hour periods of ambulatory electrocardiographic monitoring. Most strikingly, however, the larger dose of the combination of drugs was significantly more effective than all other medications, and the improvement over placebo was striking ($p < 0.0005$ for all variables, with a reduction in the area of exercise-induced ischemia as judged by precordial mapping and the frequency of ischemic events detected by ambulatory monitoring by 90 and 95% respectively, when comparing the high dose combination with placebo). In another study (50), the total work that could be performed increased by 41% when nifedipine at 30 mg/day was combined with metoprolol or alprenolol. Two trials (51,52) with verapamil and propranolol, assessing fewer variables and in one case using a single rather than a double-blind crossover study, suggest that, therapeutically, verapamil and propranolol together are also better than either drug alone. The question of adverse effects, which proved an important issue in one of these reports (52), will be discussed in a later section.

Thus, although calcium antagonists do not appear to have the same prime role in chronic stable angina as the evidence suggests they have in variant and unstable angina, they can be of subjective and objective benefit. Controlled trials are too few to permit dogmatic statements, but the question of an advantage for a beta-receptor blocking agent or calcium antagonist is problematic at best, and our own limited but intensive trial suggests that in many cases there will be advantages if a single agent, a beta-receptor blocking drug, is used (43). There are, however, attractive theoretical reasons for preferring a combination of drugs (23), and evidence favoring use of such a combination is growing. It would be useful to see whether in future trials of such a combination, each drug has a dose-sparing effect on the other so that smaller amounts of each can be used, thus possibly obviating some adverse effects.

Mechanism of Antianginal Action

Clearly, the mechanisms of benefit will vary according to whether or not organic coronary artery disease is to a greater or lesser extent primarily responsible for the decrease in blood flow during angina. In exercise duration studies with calcium antagonists, the rate-pressure product (heart rate times systolic blood pressure) is similar to that in studies with placebo; and even for a given work load no significant difference is seen, which is unlike the situation that occurs with beta-receptor blocking drugs (21,43,50). The increased flow to areas of pacing-induced ischemia (23) may help explain the almost universal benefit seen when calcium antagonists are given to patients with variant angina. This increased flow may also explain the situation in patients with chronic stable angina, in whom beta-receptor blocking drugs may have the same effect or even advantages.

Protection Against Acute Ischemic Damage

Acute ischemic damage may lead to permanent change, be this myocardial infarction in the context of impaired coronary flow, or inadequate perfusion associated with cardiopulmonary bypass. At least in part because ischemia impairs the mechanism whereby calcium is pumped out of the cell, it leads to a high cytosolic calcium concentration (53,54). This calcium overload leads to increased use of adenosine triphosphate and impairment of mitochondrial function, so that further production of this substance is decreased (53). It is therefore reasonable to see whether prevention of excess entry of calcium will protect the myocardium against ischemia; indeed, beta-receptor blocking drugs seem to owe some of their protective effect to inhibition of catecholamine-stimulated calcium influx (55). In experimental situations, this beneficial effect, in terms of demonstrable mitigation of ischemic damage, has been shown for several calcium antagonists, notably verapamil and nifedipine (56–58). A tendency toward reversal of the functional impairment produced by ischemia, as judged by tension, contractility and systolic function at rest, has also been shown with verapamil, nifedipine and diltiazem (59–61). Ischemia produces increased cellular fragility in rabbit hearts, and this is prevented by pretreatment with nifedipine (62). There is a good experimental basis, therefore, for the use of calcium antagonists for cardiopulmonary bypass, in preference to potassium chloride (63), in order to prevent reperfusion injury.

Arrhythmias

Supraventricular Arrhythmias

Supraventricular tachycardia. Just over a decade ago, we reported the results of our first systematic investigation that showed the considerable value of verapamil in the conversion of paroxysmal reentrant atrioventricular tachycardia (48) in slowing and regularizing atrial fibrillation and in sometimes correcting atrial flutter (64). The prompt action of verapamil in virtually all patients with paroxysmal supraventricular tachycardia is sometimes inhibited or antagonized by changes in autonomic tone occurring soon after initiation of the tachycardia (65). Formal comparison with crossover studies in patients with this arrhythmia showed success in 19 of 20 patients with verapamil, as opposed to only 8 of 20 given practolol (66). Successful termination of the arrhythmia by intravenous verapamil does not necessarily predict that oral prophylaxis with this agent will be effective, but failure to terminate the arrhythmia with intravenous verapamil confidently indicates that oral prophylaxis will likewise fail (67,68). *As previously indicated (49), nifedipine lacks the electrophysiologic properties of verapamil* of prolonging atrioventricular nodal conduction and ability to terminate reciprocating atrioventricular tachycardia. Our preliminary studies (69) show that the electrophysiologic properties of diltiazem and verapamil tend to resemble each other; diltiazem should therefore be considered to fall more into the category of verapamil and not to resemble nifedipine.

Atrial fibrillation and flutter. Intravenous verapamil usually produces a transient increase in the degree of atrioventricular block, conversion to sinus rhythm being rare with fibrillation and uncommon with flutter (48). Some studies (70) have shown that oral verapamil can be used to control the ventricular response satisfactorily in atrial fibrillation. Where digoxin or verapamil proves inadequate in controlling the ventricular rate during atrial fibrillation, these agents can be usefully given together (71). Because verapamil causes an increase in the serum digoxin concentration, explicable in part by a reduction in renal excretion of digoxin without reduction in glomerular filtration (72), care should be taken to adjust the dose of digoxin in patients who are simultaneously given verapamil.

Ventricular Arrhythmias

Electrophysiologic studies (73) have led to the theoretical suggestion that some ventricular arrhythmias arise because, under the influence of ischemia, myocardial cells depolarize by way of the slow as opposed to the fast inward channel, a reaction that is blocked by verapamil. Other and more recent studies (74) have contradicted this view, at least as far as the His-Purkinje system is concerned; and indeed, in other studies using models of myocardial infarction, verapamil has not proved effective (75). Of clinical relevance is the failure of verapamil to inhibit chronic recurrent ventricular tachycardia during electrophysiologic testing (76). Though some ventricular extrasystoles are suppressed by intravenous verapamil (64), this agent has not been shown to be of clinical value against more serious ventricular arrhythmias (71).

When ventricular arrhythmias arise after coronary spasm, relief of the spasm by calcium antagonists has secondary antiarrhythmic value (78); the decrease in reperfusion-induced ventricular arrhythmias seen experimentally with verapamil may be relevant to this finding (79). Once again, there appears to be a difference between verapamil and nifedipine in relation to antiarrhythmic properties (49,79), though the latter report requires corroboration in the clinical context. Indeed, experimental evidence that verapamil protects against the ventricular fibrillation produced in dogs by coronary artery occlusion or by release of this occlusion (80,81) still requires clinical validation that is difficult to achieve.

Role of verapamil. The antiarrhythmic effects of verapamil are important; in fact, this agent has been categorized as the prototype of a fourth kind of activity in the classification propounded by Vaughan Williams (82). Apart from other members of the same chemical family, diltiazem appears to be the calcium antagonist that also tends to have this effect, which is not common to all calcium antagonists as evidenced by the lack of such antiarrhythmic properties of nifedipine (49). There is a definite role for verapamil in supraventricular arrhythmias, for which it appears to be the best currently available agent in the treatment of paroxysmal supraventricular tachycardia; calcium antagonists have not proved of direct value for ventricular arrhythmias despite some theoretical suggestions that have been made.

Hypertension

It has recently been suggested that a sodium transport inhibitor might be important in hypertension and be linked with excessive entry of calcium into the vascular smooth muscle (83); in keeping with this observation is the fact that the calcium antagonists nifedipine and verapamil cause a greater reduction in blood pressure in hypertensive subjects than in normal subjects (84,85). In hypertensive patients, 30 mg of nifedipine produced a decrease of approximately 28% in both systolic and diastolic blood pressure, accompanied by an increase in heart rate of 17% and an increase in plasma renin activity; both effects were blocked by propranolol, which also caused a further slight reduction in blood pressure (86). In our own double-blind studies (85), nifedipine taken for a month (30 mg/day for 2 weeks, followed by 60 mg/day for 2 weeks) reduced supine and standing systolic and diastolic blood pressure by 15 and 20% and by 21 and 23% respectively; in these and other long-term studies there was no increase in heart rate. Important dose-dependent reductions in blood pressure also have been seen with verapamil, both in double-blind placebo-controlled crossover studies and in studies in which this agent was substituted for existing drugs; again these long-term studies were not associated with significant increases in heart rate (87–89). We and others (85,90,91) have found additional benefit, with attenuation of some of the adverse effects seen with nifedipine, when this agent has been combined with beta-receptor blocking drugs for the treatment of hypertension.

Though the use of calcium antagonists to manage hypertension has attracted less attention than has their use in the management of ischemic heart disease and arrhythmias, there is a growing body of evidence providing both theoretical and practical indication of their value, either alone or in combination with beta-receptor blocking drugs. Other interactions clearly need study in view of the large number of medications already in use for hypertension. The evidence suggests good tolerance and efficacy, and specific additional benefits in those hypertensive patients suffering from symptomatic ischemic heart disease.

Hypertrophic Cardiomyopathy

Effect on left ventricular hypertrophy. In the light, perhaps, of theoretical considerations related to increased transmembrane calcium flux in the hereditary cardiomyopathy of Syrian hamsters (92), Kaltenbach et al. (93) gave long-term oral verapamil to patients with hypertrophic cardiomyopathy whose left ventricular hypertrophy had remained unchanged or become worse while receiving propranolol; after the switch to verapamil substantial regression of hypertrophy was seen, as judged mainly by plain radiography and electrocardiographic criteria. The same workers (94) have shown similar results in longer studies on 22 patients given a mean oral daily dose of verapamil of 480 mg for an average of 15 months. In this study, some patients underwent echocardiographic assessment, and in 10 patients cardiac catheterization was repeated; the left ventricular muscle mass was decreased in 7 of these 10. From 39 patients followed up over a mean period of 26.4 months, favorable results were confirmed.

Effect on ventricular function. Exercise capacity was improved in patients with hypertrophic cardiomyopathy given verapamil, and this increased capacity was related to an improvement in the abnormal left ventricular diastolic filling seen in this condition, there being no alteration in systolic function (95). While the investigators (96) noted substantial subjective improvement during long-term treatment with verapamil, they did not see improvement in echocardiographic measurements in 31 patients treated for 1 year, an experience different from that of the German workers (94). Although there was improved systolic performance and diastolic function, as judged echocardiographically in 15 patients given sublingual nifedipine (97), the combined administration of nifedipine and propranolol appeared to be superior as judged at hemodynamic study in 12 patients (98).

Effect on arrhythmias. Although there are several reports of subjective and objective improvement, the latter in terms of cardiac function, when calcium antagonists are administered to patients with hypertrophic cardiomyopathy,

such treatment may provide only limited protection against the most lethal consequences of the disorder. In 19 patients with hypertrophic cardiomyopathy complicated by refractory arrhythmias, verapamil failed to reduce the incidence of arrhythmia, whether supraventricular or ventricular, in contradistinction to another antiarrhythmic agent, amiodarone (99). An important area in which theoretical considerations had suggested additional value thus has not been confirmed in practice.

Heart Failure

Even though the direct intracoronary administration of nifedipine produces a negative inotropic effect, such changes are overcome on intravenous injection by virtue of the reflex increases in contractility and heart rate that occur as a result of lowering systemic arterial pressure (100). After sublingual administration of nifedipine to patients with ischemic heart disease with depressed left ventricular function, no discernible adverse effects were noted (101). In 14 patients with left ventricular dysfunction subjected to an exercise test before and 60 minutes after taking 30 mg of nifedipine sublingually, pulmonary artery pressures, which did not change at rest, decreased significantly during exercise, probably owing to a shift in left ventricular pressure-volume relations (102). Despite these promising observations and occasional success in the clinical management of heart failure (103), great prudence is necessary while the role of such agents receives much more careful and extensive evaluation.

Primary Pulmonary Hypertension

The treatment of primary pulmonary hypertension with vasodilators has produced mixed results. Some workers (104) reported benefit with oral nifedipine on the basis of an initial favorable acute hemodynamic response. Others (105,106), and indeed these original authors, have now reported that such effects are inconsistent, that a positive hemodynamic response does not always predict clinical benefit and that right ventricular failure might be induced. It is conceivable that greater systemic vasodilatation of healthy vessels may contribute toward such adverse effects, though individual cases may show benefit.

Side Effects

Sinoatrial depression. Understandable concern has arisen since the occasional observation of sinoatrial depression in patients given verapamil intravenously for the termination of paroxysmal supraventricular tachycardia, but the explanation is usually clear: either the patient has concomitantly received beta-adrenergic blocking agents or has sinoatrial disease (48). Verapamil therefore should not be given under these circumstances (107), and it is prudent that on the first occasion it is given to a patient with paroxysmal supraventricular tachycardia, appropriate treatment be available in case sinoatrial disease is present. We have seen no evidence of sinoatrial depression with nifedipine whether given alone or in combination with propranolol (85). Should hypotension occur after intravenous verapamil is given for paroxysmal supraventricular tachycardia, it is usually mild and transient (64).

Negative inotropic effects. Although concern has been expressed about the negative inotropic effects of calcium antagonists, these effects have not caused major difficulty; indeed, verapamil has been given without ill effect to patients with myocardial infarction (108). As already indicated, any negative inotropic effect is usually counterbalanced by reflex sympathetic drive (100–102). Fears have been expressed that the simultaneous administration of a beta-receptor blocking agent might have ill effects, perhaps by interfering with such responses; though there are isolated case reports from which one might suspect the combination of nifedipine and beta-receptor blocking agents to cause hypotension or heart failure (109–112), this has not, in practice, proved an important problem (85). Many of these reports are anecdotal and lack full hemodynamic information and should be balanced against careful observations made to test the situation. In one such study (113), 12 patients underwent cardiac catheterization for the investigation of chest pain; though 8 were found to have coronary artery disease, none was shown to have any impairment of left ventricular function. The heart rate was then kept constant by right atrial pacing at 100/min. While nifedipine depressed the peak first derivative of left ventricular pressure (dP/dt), it also significantly decreased systemic vascular resistance. Nifedipine therefore increased cardiac output in association with arterial dilatation despite evidence for a negative inotropic effect; once again, the intrinsic negative inotropic effects under these circumstances need assessment in patients with impaired myocardial output, an aspect we are exploring at present. This is strongly supported by a careful study (114) in which combined treatment with acebutolol and nifedipine in patients with chronic coronary artery disease was assessed: in 21 patients with angiographically documented coronary artery disease and stable angina, simultaneous hemodynamic and radionuclide ventriculographic measurements were made at rest and during exercise before treatment, as well as 30 minutes after the administration of nifedipine or acebutolol, or the combination. The negative inotropic effects of the beta-adrenergic blocking drug were balanced by the nifedipine and no adverse effects were seen in patients with borderline heart failure.

While Leon et al. (51) noted no adverse effects from the combination of oral verapamil and propranolol in 11 patients with angina, there may be some concern when myocardial function is depressed (115), and it is worrying that 7 of 40 patients similarly treated developed hypotension or heart failure and that sinus node depression was observed appar-

ently in the short term in 4 additional patients (52). Significant negative inotropic and chronotropic effects, but no untoward symptoms, were also seen in 15 patients during a 3 day trial of this combination (116). Clearly, however, more careful and prolonged studies under clinical conditions will be required to assess the benefits and potential disadvantages of such combinations.

Specific adverse effects that also require consideration are the occasional anecdotal reports of chest pain following nifedipine, which are difficult to assess (117), and problems with verapamil in hypertrophic cardiomyopathy. Epstein and Rosing (118) encountered serious hemodynamic complications in patients with this disorder and caution against use of verapamil in patients who have a high pulmonary capillary wedge pressure, paroxysmal nocturnal dyspnea or orthopnea in the presence of left ventricular outflow obstruction, or sinoatrial or atrioventricular disease unless a pacemaker has been implanted.

Noncardiac untoward effects. These are few; in the case of verapamil, constipation may be a nuisance, and with nifedipine, ankle edema apparently resulting from peripheral vasodilatation (85). Interestingly, in this study we noted that ankle edema was seen in fewer patients taking the combination of nifedipine and propranolol, and also that those who developed coldness of the limbs with propranolol treatment were less troubled by it while taking the combination of drugs.

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